



TITLE:

Barrier dysfunction in allergy

AUTHOR(S):

Kabashima, Kenji; Izuhara, Kenji

CITATION:

Kabashima, Kenji ...[et al]. Barrier dysfunction in allergy. *Allergology International* 2018, 67: 1-2

ISSUE DATE:

2018-01

URL:

<http://hdl.handle.net/2433/230790>

RIGHT:

© 2017, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>



Editorial

Barrier dysfunction in allergy

In *Allergology International* (AI) Vol. 67, Issue 1, we feature a set of review articles entitled “Barrier dysfunction in allergy” as well as original articles and letters to the editor. We believe that this issue will be of great help in understanding how barrier disruptions are associated with the onset of allergy in barrier organs, which may lead to the prevention of allergic diseases.

The barrier organs—such as the skin, lung, gut, and nasal cavity—cover the entire body and protect us from the external environment. When these barriers are impaired, external toxins penetrate the body and induce inflammation to defend against them. Over the last decade, many studies have demonstrated that barrier dysfunction is a critical component of allergy.^{1–3} In particular, inherited defects in epidermal barrier proteins, such as filaggrin, facilitate the interaction of external antigens with skin-resident immune cells, driving local inflammation that can also lead to systemic immune responses.^{4,5} This is the “outside-in” hypothesis of atopic dermatitis pathogenesis, and it helps to explain why atopic dermatitis sufferers have an increased risk of developing food allergies, asthma, and allergic rhinitis later in life, known as the “atopic (allergic) march”.⁶ These observations suggest that maintaining the skin barrier function is important for both effectively managing atopic dermatitis and preventing subsequent allergic diseases.

In this review article series, Egawa and Kabashima summarize how the physical barrier of the skin is organized and review its link to the pathogenesis of skin allergic diseases, such as atopic dermatitis, from the perspective of the stratum corneum components: 1) filaggrin metabolism, 2) cornified envelope, 3) intercellular lipids, 4) corneodesmosome, and 5) corneocyte desquamation.⁷ Gon and Hashimoto summarize the pathogenesis of bronchial asthma, characterized by the hyper-responsive, chronically inflamed airways. Damage to the barrier functions of the airway epithelium enhances mucosal permeability of foreign substances, leading to the release of epithelial cytokines (e.g. TSLP, IL-25, and IL-33), which then activates dendritic cells, Th2 cells, and type 2 innate lymphoid cells to cause allergic airway inflammation.⁸ Fukuoka and Yoshimoto summarize the functions of tight junctions, a cell–cell junctional complex located on the apical side of epithelial cells. And they review an interesting observation that diesel exhaust particles, the main component of particulate matter 2.5 (PM2.5), exacerbated allergic rhinitis in a mouse model through tight junction disruption.⁹ These findings suggest that controlling barrier functions is important to prevent allergies, which is in line with a paradigm shift away from avoidance and delayed

introduction of allergenic foods. Natsume and Ohya show the increased importance of preventing eczema/atopic dermatitis in infancy.¹⁰ Two randomized controlled trials using emollients showed successful results in preventing infant atopic dermatitis.^{11,12} Taken together, recent findings on barrier dysfunctions in allergy have revealed the pathogenesis of allergic diseases and pointed the way to novel strategies to control allergic diseases.¹³

During the 2015 enterovirus D68 epidemic, both an unusual cluster of children with acute flaccid paralysis and a high rate of hospitalization of asthmatic children were observed. Korematsu *et al.* report the results of a nationwide retrospective survey conducted by the Japanese Society of Pediatric Allergy and Clinical Immunology. Their analysis confirms the association between the unusual increase in acute asthma hospitalizations of children and the enterovirus D68 epidemic in September 2015 in Japan.¹⁴ To verify a causative role for a respiratory virus in exacerbating asthma in children, surveillance systems for asthma and respiratory infectious pathogens have been shown to be essential.

The pathogenesis of mild persistent asthma in children, and optimal treatments for it, remain elusive. Nagao *et al.* performed a randomized, controlled trial of treatment of preschool children with mild persistent asthma using a leukotriene receptor antagonist (LTRA), montelukast, daily for 48 weeks [recommended by Japanese Guideline for Childhood Asthma (JGCA)]¹⁵ or as-needed β_2 -agonist(s) (recommended by GINA and EPR-3 guidelines).^{16–18} LTRA significantly reduced acute exacerbations and the percentage of children needing step-up treatment. These results not only demonstrated the superiority of the JGCA guideline, but also suggested the involvement of cysteinyl leukotrienes in the exacerbation and progression of childhood asthma.

Oguma *et al.* report the first nationwide survey of allergic bronchopulmonary aspergillosis (ABPA) in Japan, one of the largest studies examining the clinical characteristics of this disease worldwide.¹⁹ ABPA is an allergic pulmonary disease characterized by a hypersensitivity reaction to *Aspergillus* species colonizing the airways. They summarized 358 cases meeting the criteria for possible ABPA-central bronchiectasis (ABPA-CB) taken from 499 physician-diagnosed cases reported by 132 clinical centers. This survey identified several unique clinical characteristics of ABPA in Japan compared to other countries: late onset (median: 57 years); relatively lower serum IgE levels, particularly in late-onset patients; and frequent recurrences/flare (48%). These patients do not meet the current diagnosis criteria; therefore, some modification of these criteria is needed for this phenotype of ABPA.

Japanese cedar pollinosis, including allergic rhinitis and conjunctivitis, has been considered a national affliction in Japan,

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2017.12.001>

1323–8930/Copyright © 2017, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

with a prevalence of >25%.²⁰ Fukuda *et al.* demonstrated that feeding mice suffering from allergic conjunctivitis caused by Japanese cedar with transgenic rice expressing two major allergens of Japanese cedar pollinosis, Cry j 1 and Cry j 2, ameliorated the disease.^{21,22} The allergens of Japanese cedar pollinosis are expressed as fragmented and shuffled sequences in the transgenic rice in order to eliminate IgE reactivity, not to cause adverse anaphylactic reaction. The rice-based edible allergen vaccine for Japanese cedar pollinosis is potentially effective and safe for oral immunotherapy in people suffering from this condition.

We offer our appreciation to all the authors for their contributions to the present issue of Allergy International.

Conflict of interest

The authors have no conflict of interest to declare.

Kenji Kabashima, Associate Editor, Allergy International^a,
Kenji Izuhara, Editor-in-Chief, Allergy International^{b,*}

^a Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

^b Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, Saga, Japan

* Corresponding author. Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, 5-1-1 Nabeshima, Saga 849-8501, Japan.

E-mail address: kizuhara@cc.saga-u.ac.jp (K. Izuhara).

References

- Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;**38**:441–6.
- Elias PM, Schmuth M. Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. *Curr Allergy Asthma Rep* 2009;**9**:265–72.
- Cork MJ, Danby SG, Vasilopoulos Y, Hadgraft J, Lane ME, Moustafa M, et al. Epidermal barrier dysfunction in atopic dermatitis. *J Invest Dermatol* 2009;**129**:1892–908.
- Egawa G, Kabashima K. Multifactorial skin barrier deficiency and atopic dermatitis: essential topics to prevent the atopic march. *J Allergy Clin Immunol* 2016;**138**:350–8. e1.
- Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity. *J Dermatol Sci* 2013;**70**:3–11.
- Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;**112**:S118–27.
- Egawa G, Kabashima K. Barrier dysfunction in the skin allergy. *Allergol Int* 2018;**67**:3–11.
- Gon Y, Hashimoto S. Role of airway epithelial barrier dysfunction in pathogenesis of asthma. *Allergol Int* 2018;**67**:12–7.
- Fukuoka A, Yoshimoto T. Barrier dysfunction in the nasal allergy. *Allergol Int* 2018;**67**:18–23.
- Natsume O, Ohya Y. Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction. *Allergol Int* 2018;**67**:24–31.
- Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014;**134**:824–30. e6.
- Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014;**134**:818–23.
- Nomura T, Kabashima K. Advances in atopic dermatitis in 2015. *J Allergy Clin Immunol* 2016;**138**:1548–55.
- Korematsu S, Nagashima K, Sato Y, Nagao M, Hasegawa S, Nakamura H, et al. "Spike" in acute asthma exacerbations during enterovirus D68 epidemic in Japan: a nation-wide survey. *Allergol Int* 2018;**67**:55–60.
- Hamasaki Y, Kohno Y, Ebisawa M, Kondo N, Nishima S, Nishimura T, et al. Japanese guideline for childhood asthma 2014. *Allergol Int* 2014;**63**:335–56.
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. <http://ginasthma.org/archived-reports/>. Accessed August 31, 2016.
- National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma-Full Report 2007. <http://www.nhlbi.nih.gov/health-pro/guidelines/>. Accessed August 31, 2016.
- Nagao M, Ikeda M, Fukuda N, Habukawa C, Kitamura T, Katsunuma T, et al. Early control treatment with montelukast in preschool children with asthma: a randomized controlled trial. *Allergol Int* 2018;**67**:72–8.
- Oguma T, Taniguchi M, Shimoda T, Kamei K, Matsuse H, Hebisawa A, et al. Allergic bronchopulmonary aspergillosis in Japan: a nationwide survey. *Allergol Int* 2018;**67**:79–84.
- Yamada T, Saito H, Fujieda S. Present state of Japanese cedar pollinosis: the national affliction. *J Allergy Clin Immunol* 2014;**133**:632–9. e5.
- Fujimura T, Kawamoto S. Spectrum of allergens for Japanese cedar pollinosis and impact of component-resolved diagnosis on allergen-specific immunotherapy. *Allergol Int* 2015;**64**:312–20.
- Fukuda K, Ishida W, Harada Y, Wakasa Y, Takagi H, Takaiwa F, et al. Efficacy of oral immunotherapy with a rice-based edible vaccine containing hypoallergenic Japanese cedar pollen allergens for treatment of established allergic conjunctivitis in mice. *Allergol Int* 2018;**67**:119–23.

Received 17 November 2017